Non-small cell lung cancer

Non-small Cell Lung Cancer

Eva Szabo, MD
Chief, Lung and Upper Aerodigestive Cancer Research Group
Division of Cancer Prevention, NCI

NIH NATIONAL CANCER INSTITUTE

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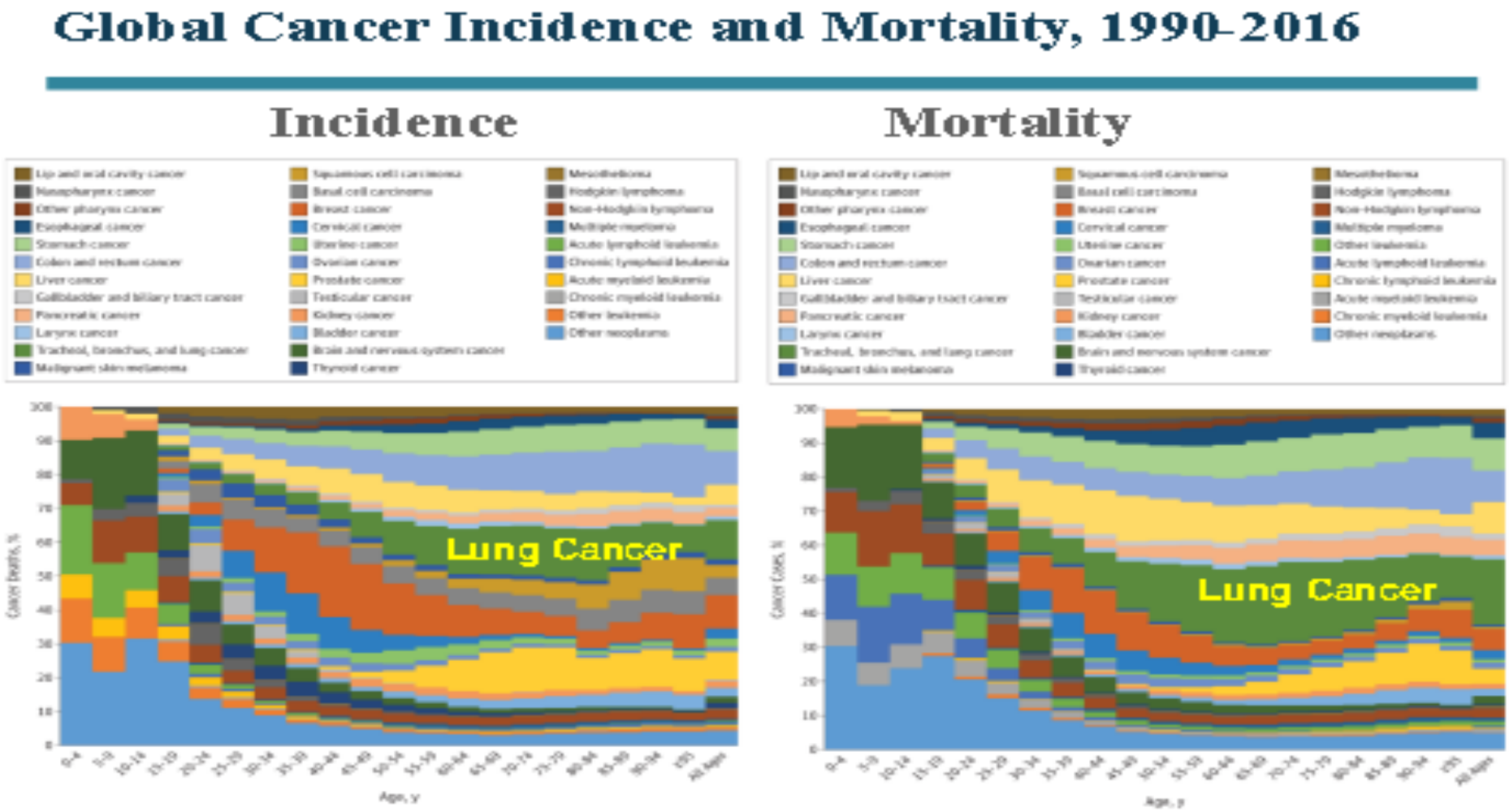
Cancer incidence and mortality



Fitzmaurice C et al., JAMA Oncol 2018;epub

US cancer statistics

US Lung Cancer Statistics, 2020

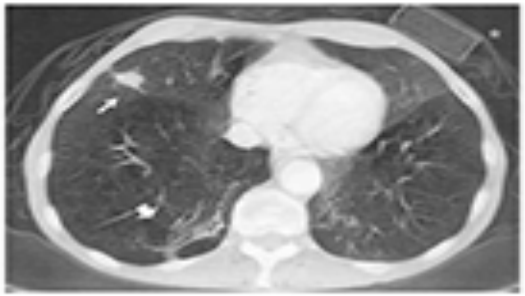
- 228,820 estimated new cases (lung and bronchus)
- 135,720 estimated deaths
- leading cause of cancer deaths
  - greater than breast+prostate+colon
  - death rate per 100,000 decreasing (90.56 in 1990; 67.45 in 2006)
    - Incidence declining in men since mid-1980's, women since mid-2000's
- 20% five year survival
  - 5% in 1950's, 12% in 1970's

26% of all male cancer deaths, 25% of all female cancer deaths

https://www.cancer.org/research/cancer-facts-statistics/all-cancer-facts-figures/cancer-facts-figures-2020.html

Risk factors

Risk Factors

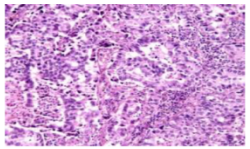
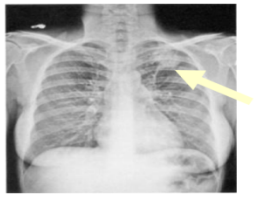
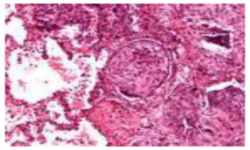
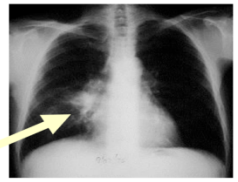
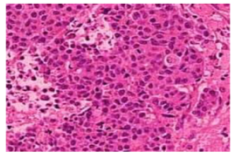
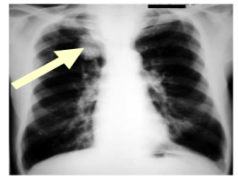
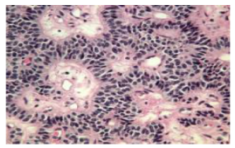


- Tobacco, tobacco, tobacco (85% lung ca.)
  - Including passive smoking
  - Prior aerodigestive malignancy
  - COPD
- Other exposures
  - Asbestos, radon, polycyclic aromatic hydrocarbons, chromium, nickel, inorganic arsenic – mining, ship building, oil refining
- Genetic predisposition
  - Familial lung cancer – Germline mutations - EGFR T790M
    - Bell et al., Nat Gen 2005;37:1315
  - 15q24-25.1 – nicotinic acetylcholine receptor subunits CHRNA3 and CHRNA5, OR=1.3, attributable risk ~14%
    - Amos et al., Nat Gen 2008;40:616, Hung et al. Nature 2008;452;633, Thorgeirsson et al. Nature 2008;452:638
  - CH3NA3/5 is also susceptibility locus for COPD
    - Pillai et al. PLoS Genet 2009;5:1

Pathology: NSCLC

Pathology: Non-small Cell Lung Cancer

- **Adenocarcinoma, inc bronchoalveolar**
  - **40%**
- **Squamous cell carcinoma**
  - **20%**
- **Large cell carcinoma**
  - **15%**
- **Others (carcinoid, etc.)**


Lung carcinogenesis

The Continuum of Lung Carcinogenesis

Opportunities for Intervention

Normal → Hyper/Metaplasia → Dysplasia → Early-Late Cancer

Prevention

Early Detection

Treatment

Treatment Strategies for Lung Cancer

- **Treatment based on stage:**
  - **Early stage (Stage I) – surgery**
  - **Early stage (Stage II, IIIA resected)-surgery + adjuvant chemo**
  - **Regional spread (IIIA/IIIB) – combined modality (chemoradiation; +/- surgery for IIIA)**
  - **Metastatic (IIIB "wet"/IV)– chemotherapy, radiation as needed for local control, occasional resection of isolated metastases**
- **Small cell lung cancer: chemotherapy (+thoracic radiation for limited stage; prophylactic cranial radiation to prevent brain mets)**

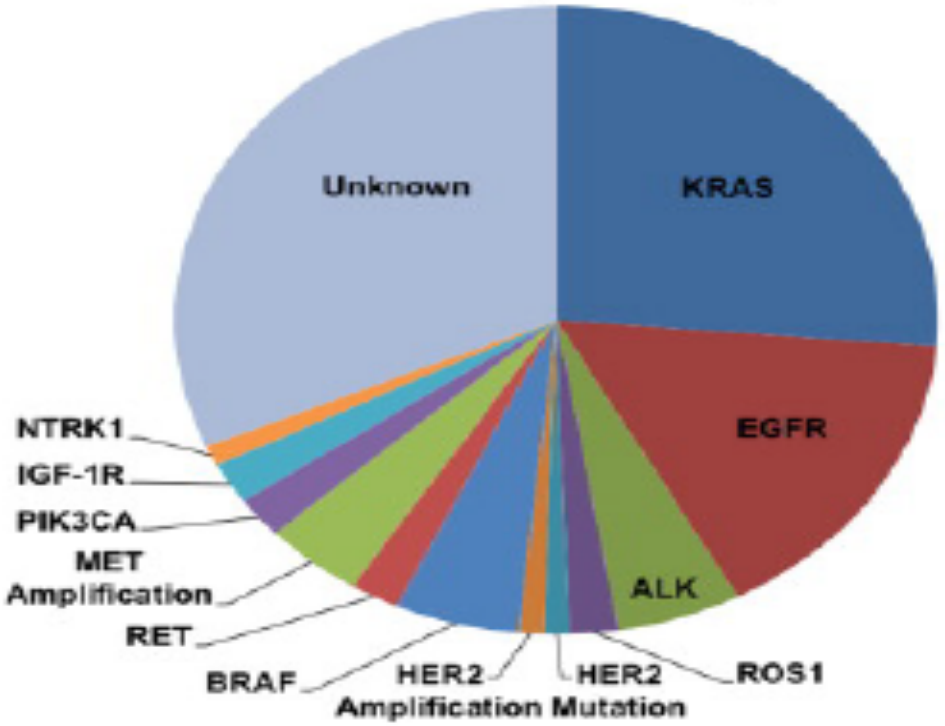
Treatment options

Treatment Options for Metastatic NSCLC

- **Chemotherapy**
  - **Platinum doublets, iv**
  - **Adjuvant, metastatic disease**
  - **Still a mainstay of treatment**
- **Targeted therapy**
  - **For minority of patients with targetable mutations**
  - **Oral therapies, better tolerance**
  - **Extended survival**
- **Immunotherapy**
  - **Now a definitive role, frontline and second line**

Personalizing Therapy for NSCLC

Personalizing Therapy for NSCLC
Genetic Abnormalities in Lung Adenocarcinoma



Targetable mutations/gene fusions

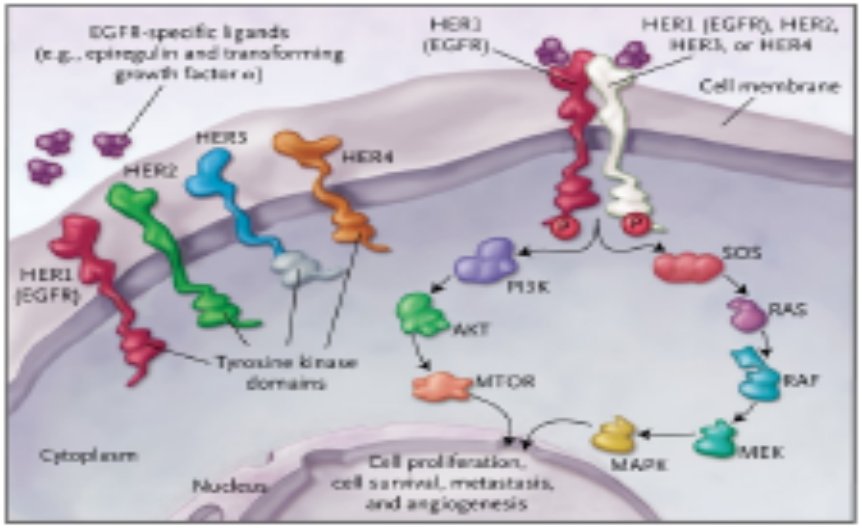
- EGFR
  - multiple drugs
- ALK
  - multiple drugs
- ROS1
  - crizotinib
- BRAF-V600E only
  - dabrafenib/trametinib
- RET
  - Experimental drugs (BLU-667)
- NTRK
  - larotrectinib
- MET ex 14 skipping
  - crizotinib
- HER2/Neu – exon 20 mutations
  - HER2 antibodies + chemo

Response rates 50-80%

Berge and Doebele Sem Oncol 2014; Hunter et al. Nature 2004; Heinmoller P et al. Clin Cancer Res 2003; Drilon A et al. JCO 2016 suppl; Drilon A NEJM 2018

EGFR and NSCLC

EGFR as a Target for NSCLC

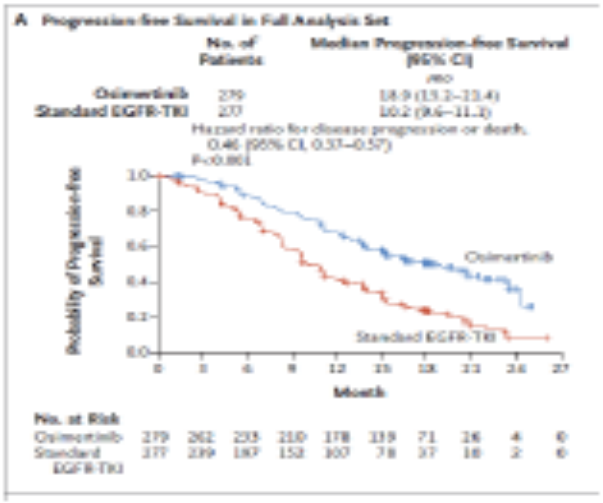


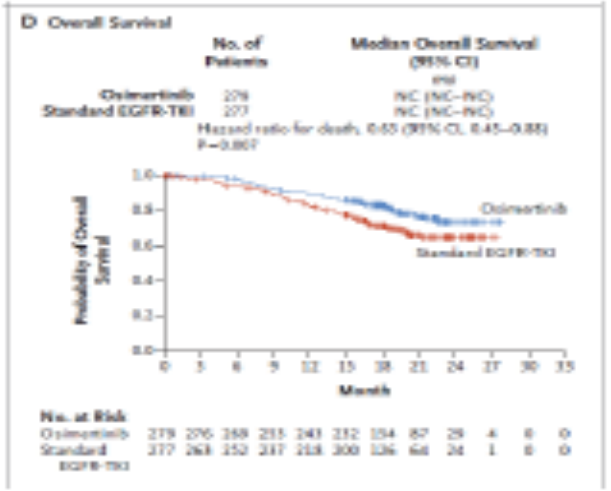
- Epidermal growth factor receptor (EGFR) mutated in ~15% NSCLC
- Oncogenic driver; primarily in non-smokers
- Targeted therapies tyrosine kinase inhibitors (TKIs) highly active
  - 60-80% response rates EGFR-MT disease
  - Progression-free survival 10-14 months (c/w chemo 4-6 months)
  - Median survival 30 vs. 24 months with chemo
    - Maemondo et al N Engl J Med 2010;362:2380
- Multiple TKIs approved for frontline use; 3rd generation TKI (osimertinib) superior
- Mechanisms of resistance well understood (T790M; osimertinib)

Osimertinib

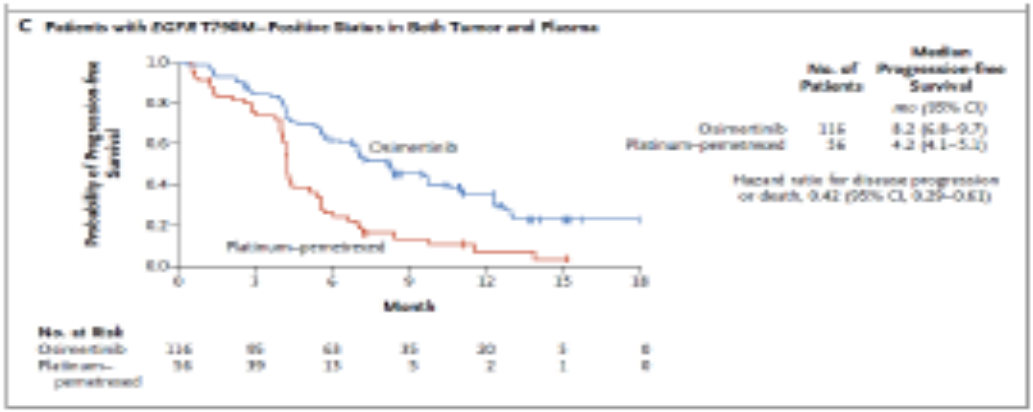
Osimertinib in Chemotherapy-naïve Patients

No prior Rx





Prior frontline TKI but no prior chemo

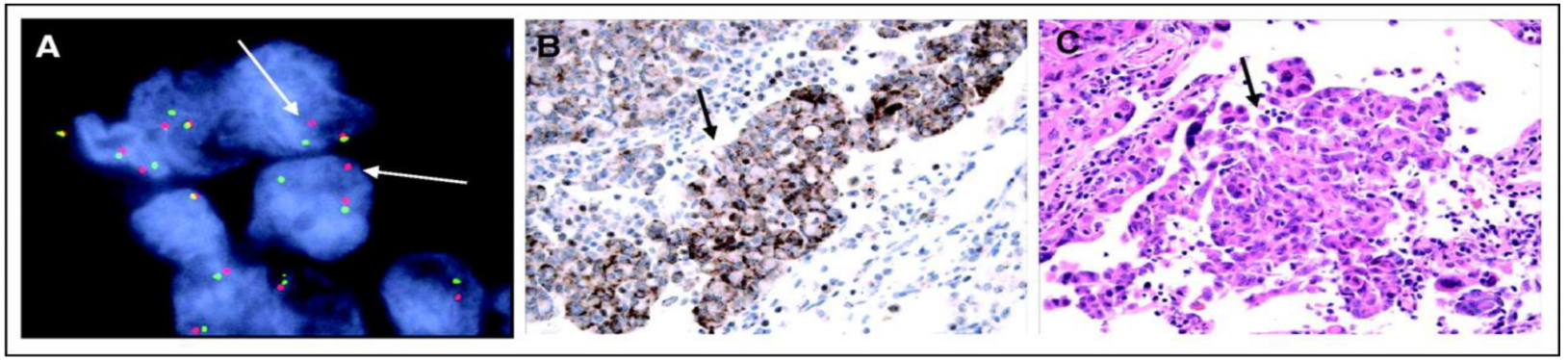


Mok T S et al. NEJM 2016
Soria J C et al. NEJM 2017

EML4-ALK

EML4-ALK Fusion Gene as a Target for NSCLC

- Identified in 2007
- ~5% NSCLC, mainly never smokers
- Striking response to inhibitor – crizotinib- 57% RR, 33% stable disease (FDA approved)
  - Kwak EL et al. NEJM 2010;363:1693
- 2nd line agent approved (ceritinib), 56% RR
  - Shaw AT, et al. NEJM 2014;370:1189
- Multiple mechanisms of resistance

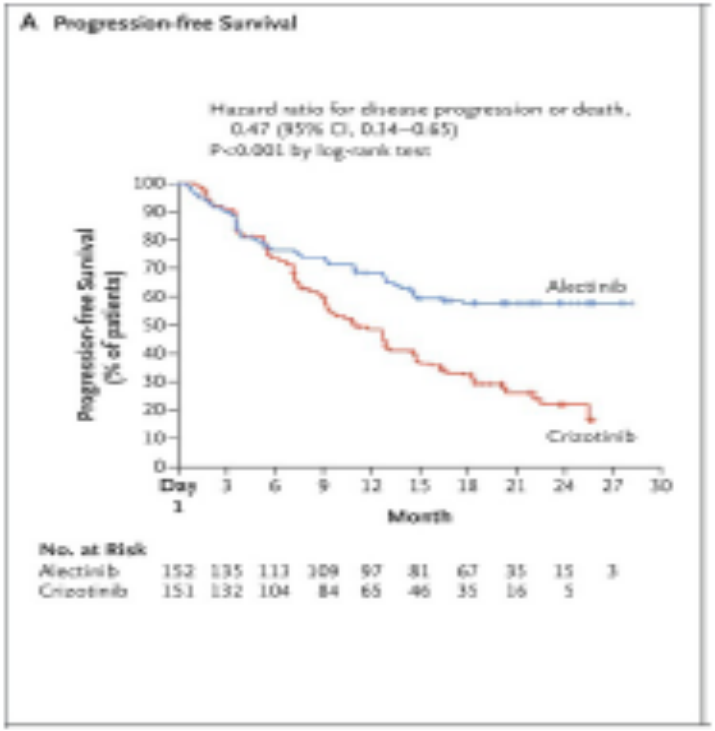


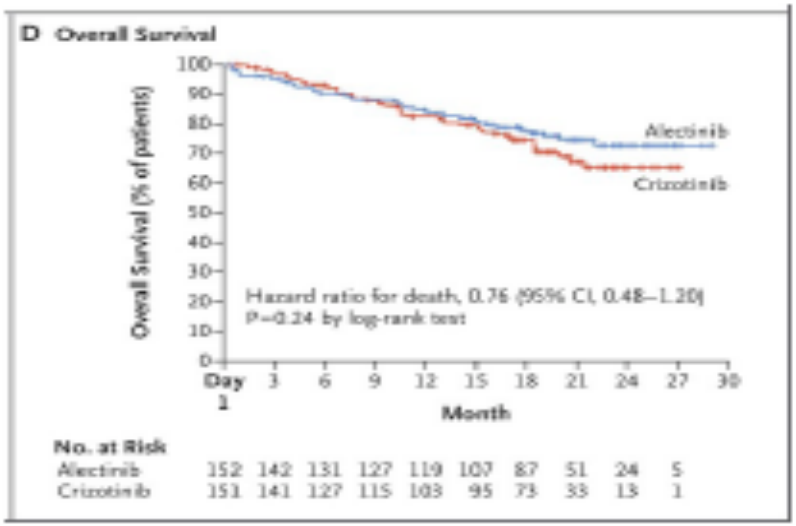
Shaw AT et al., JCO 2009;27:4247

Alectinib

Alectinib for EML4-ALK Translocated NSCLC

-Progression-free survival 34.8 mths alectinib vs. 10.9 mths crizotinib
-long term survival better with alectinib



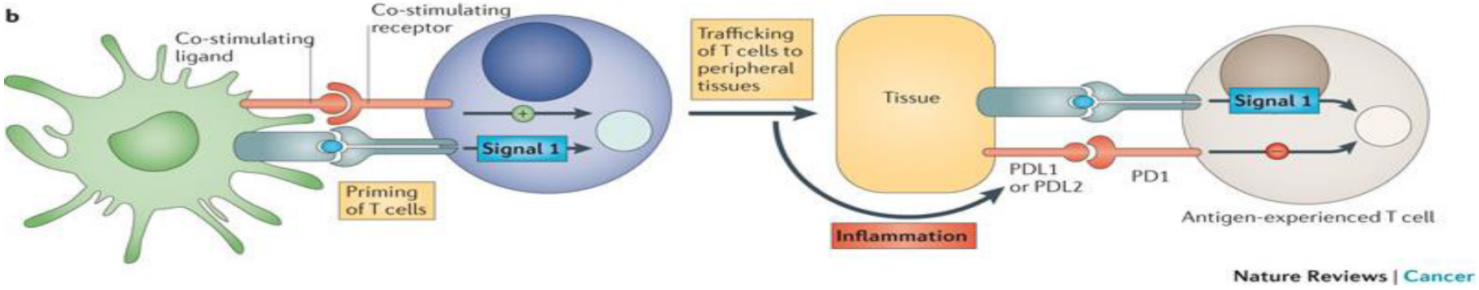


Peters S et al. N Engl J Med 2017;377:829
Camidge DR et al. J Thorac Oncol 2019;14:1233

New Approaches-Immunotherapy

New Approaches - Immunotherapy

- PD-1
  - T-cell co-inhibitory receptor, regulates T-cell activation
  - Main role: to limit activity of T cells in peripheral tissues during inflammatory response to infection and to limit autoimmunity
  - ligands PD-L1 (frequently expressed on tumors) and PD-L2
  - Blockade of PD-L1/PD-1 interaction potentiates immune response (to tumor)

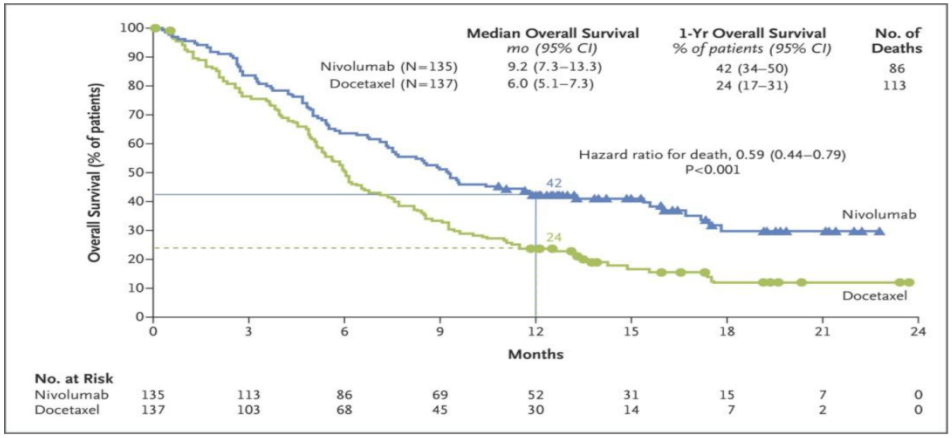


Pardoll D Nat Rev Cancer 2012;12:252

Immunotherapy

New Approaches - Immunotherapy

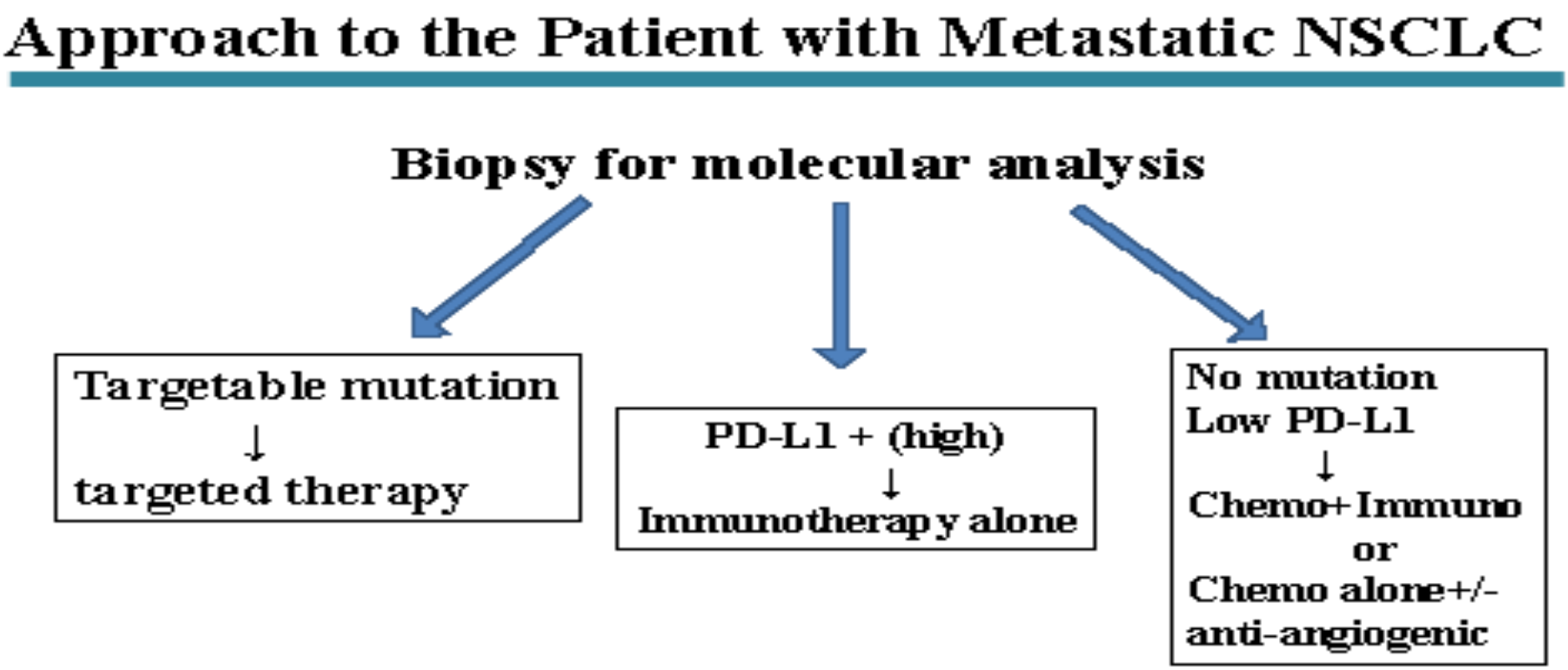
- **Anti-PD-1 antibodies approved for 2nd line NSCLC; nivolumab and pembrolizumab (PD-L1+)**
  - **~20% response rate (vs. 10% docetaxel)**
  - **~3 month improved overall survival nivolumab c/w docetaxel**
  - **Long term responses (median duration 12.5 mths with pembro)**



Squamous, nivolumab:
-Brahmer J et al. N Engl J Med 2015;373:123-135.

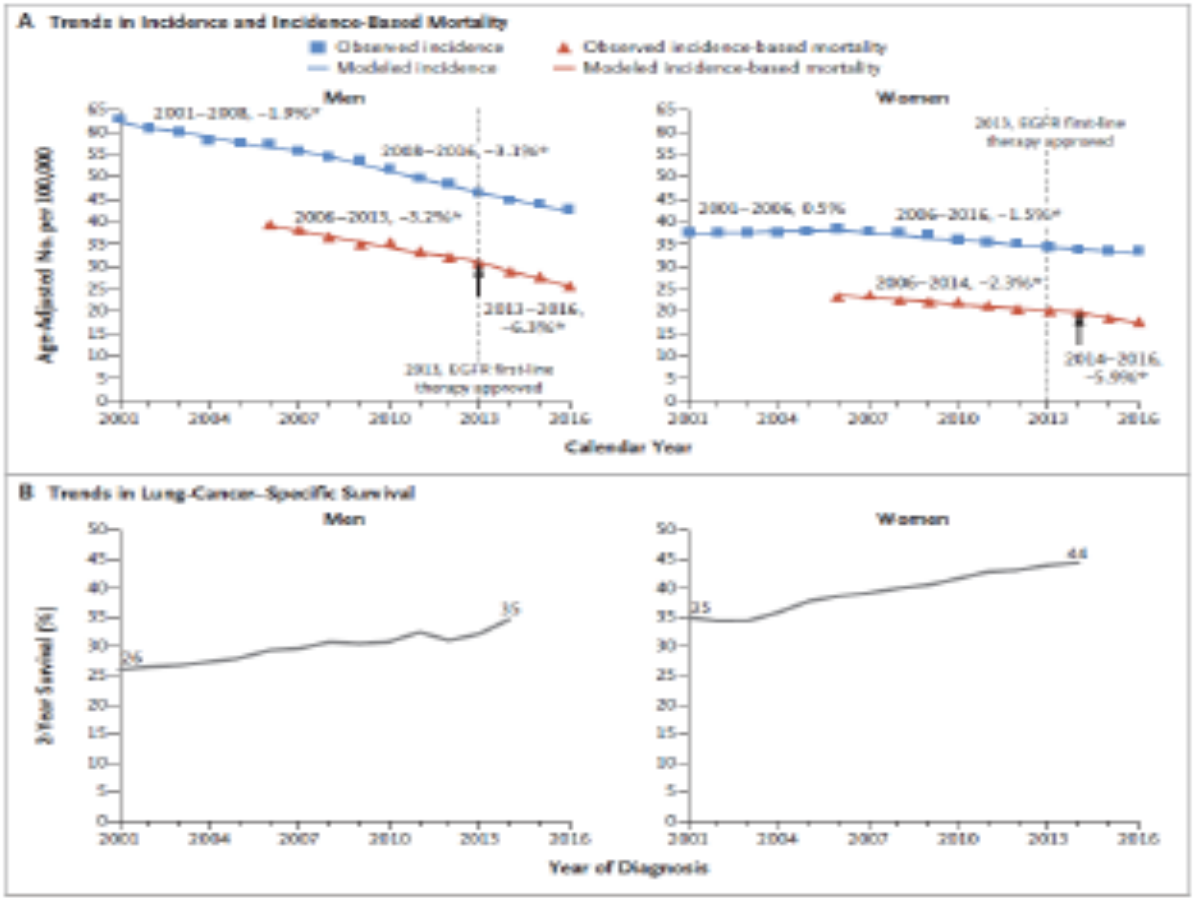
Non-squamous, nivolumab: Borghaei H et al. N Engl J Med 2015;373:1627-1639
Any NSCLC, pembrolizumab: Garon EB et al. N Engl J Med 2015;372:2018-2028

Clinical approach



NSCLC mortality

↓ Mortality from NSCLC with Improved Therapy



Mortality decreased faster than incidence

- 2013-2016 -Mortality ↓6.3% annually (men)
- 2008-2016 - Incidence ↓3.1% annually (men)
- Lung cancer specific survival improved from 26% to 35% from 2001 to 2016
- Similar in women, across all races/ethnic groups
- For SCLC, decreased mortality was same as decreased incidence
- **Conclusion: treatment advances (esp. targeted therapies) responsible**

Howlader N et al., NEJM 2020; 383:640

Approaches to reducing cancer morbidity and mortality

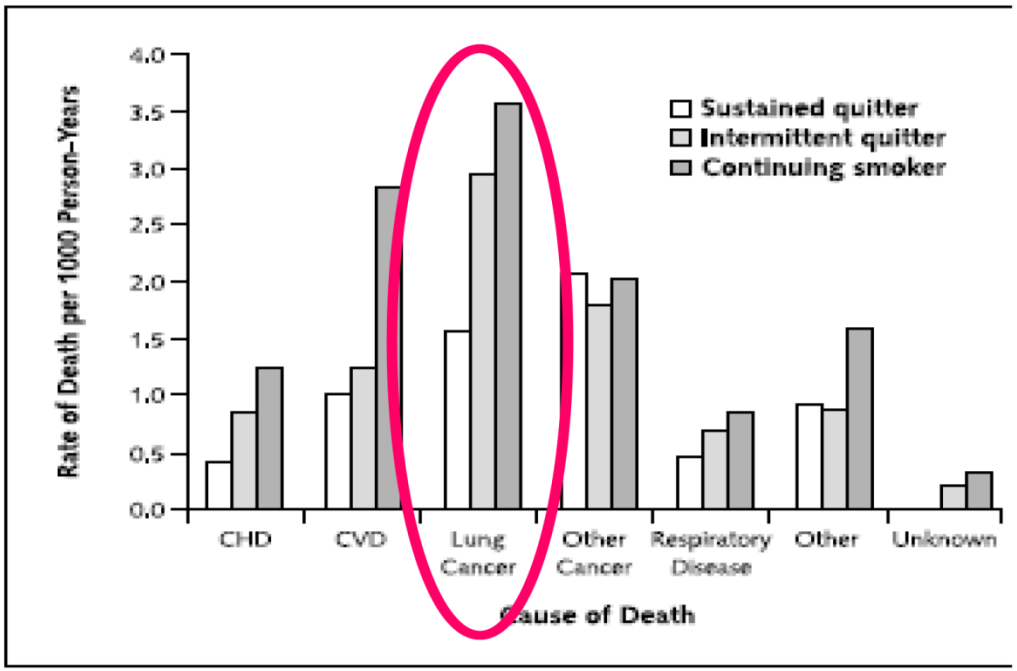
- **Prevention (primary, secondary, tertiary)**
- **Early detection**

- **Better therapeutics**

Smoking Cessation and Lung Cancer

Effect of Smoking Cessation on Lung Cancer Death

Lung Health Study, 14.5 yr F/U



Anthonisen et al., Ann Intern Med 142:233, 2005

Lung carcinogenesis

The Continuum of Lung Carcinogenesis

Opportunities for Intervention

Normal → Hyper/Metaplasia → **Dysplasia** → Early-Late Cancer

Prevention

Early Detection

Treatment

Cancer Chemoprevention

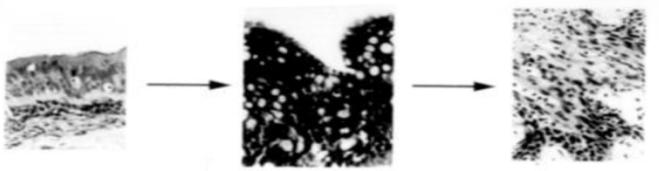
The use of natural or synthetic agents to suppress or reverse carcinogenesis

- **Regress existing neoplastic lesions (treat intraepithelial neoplasia)**
- **Prevent development of new neoplastic lesions (preneoplastic and cancer)**
- **Suppress recurrence of neoplastic lesions**

Lung Cancer Prevention

Rationale for Lung Cancer Prevention

- **Metastatic cancer is rarely curable**
  - **US lung cancer 5 yr survival is ~15% (5% 1950's, 13% 1970's)**
- **Cancer is preventable**
  - **P1, STAR breast cancer prevention trials with tamoxifen and raloxifene**
    - *Fisher B et al., JNCI 1998;190:1371; Vogel, VG et al., JAMA 2006;295:2727*
  - **Multiple animal studies with multiple agents**
- **Long preclinical phase with increasing histologic and molecular abnormalities, identifiable populations at risk**



Lung premalignancy

Evolution of Lung Premalignancy

Normal → Hyperplasia/Metaplasia → Dysplasia → Cancer

Mild/Moderate/Severe/CIS

Squamous (central)

Adenomatous (peripheral)

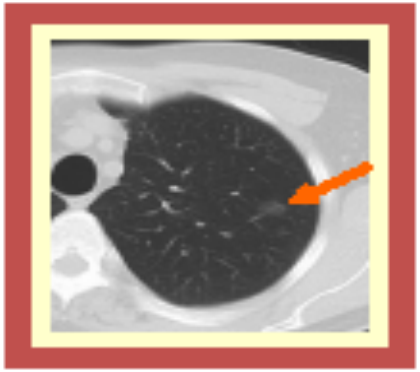
Bronchial dysplasia

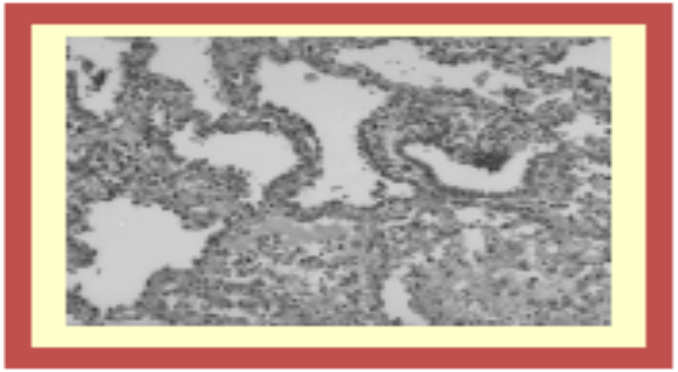
Squamous Cell Carcinoma Precursor: Bronchial Dysplasia

- Progression to cancer based on bronchoscopic dx, median 2-3 yr f/u *(Bota et al, Am J Respir Crit Care Med 2001:164;1688; Venmans et al., Chest 2000:117;1572; Breuer et al. Clin Cancer Res 2005:11;537)*
  - Metaplasia: 37-42% regress, 2-9% CIS/cancer (at 4-59 mths)
  - Mild/moderate dysplasia: 37-64% regress, 9% CIS/cancer (at 7-57 mths)
  - Severe dysplasia: 41-52% regress, 32% CIS/cancer (1-32 mths)
  - Carcinoma in situ: 56% progress at site (44% also had severe dysplasia or CIS elsewhere)
- 164 pts. with low or high-grade lesions *(Van Boerdonk et al., Am J Respir Crit Care Med 2015;192:1483)*
  - 33.5% developed invasive cancer, median 16.5 mths
  - 41% cancers developed from abnormal site, 59% from other sites (central or peripheral)
  - High grade lesions assoc with cancer; COPD and prior hx lung ca assoc with OS
- *Bronchial dysplasia both precursor and risk marker for abnormal field*

Atypical adenomatous hyperplasia

Adenocarcinoma Precursor: Atypical Adenomatous Hyperplasia (AAH)





- **Natural history not well understood**
- **Localized ground glass opacities on CT:**
  - AAH 25%; bronchoalveolar ca 50%; invasive adenoca 10%; fibrosis 15%
    - *Nakajima et al., J Comput Assist Tomogr 2002;26:323*
  - AAH 63%; bronchoalveolar ca 34%; scar 3%
    - *Ohtsuka et al., Eur J Cardio-Thor Surg 2006;30:160*

Non-solid nodules

Non-Solid Nodules – Natural History

- Prospective trial, 795 patients with 1229 subsolid nodules (GGNs, ≤3cm, solid component ≤5 mm)
  - f/u 4.3±2.5 years
  - 1046 pure GGN → 5.4% became part solid
  - 81 heterogeneous GGN → 19.8% became part solid
  - Resected nodules (in 80 patients)
    - 35/997 pure GGNs (9 MIA, 21 AIS, 5 AAH)
    - 7/78 heterogeneous GGNs (5 MIA, 2 AIS)
    - 49/174 part solid GGNs (12 invasive, 26 MIA, 10 AIS, 1 AAH)

  – *1% of all nodules became invasive cancer (all were part solid)*

  – *3.3% became MIA, 2.7% AIS, 0.5% AAH*

Kakinuma et al., J Thor Oncol 2016;11:1012

Targeting inflammation

Targeting Inflammation for Lung Cancer Prevention: Rationale

- **Animal data showing role for steroids in cancer prevention**
  - **1970's – skin**
  - **Early 1990's – lung (oral steroids)**
  - **Late 1990's – lung (inhaled steroids)**
- **Epidemiology/Human data –**
  - **Mainly negative (but studies of short exposure duration)**
  - **VA cohort with COPD (n=10,474) – HR 0.39 (95% CI, 0.16-0.96)**
    - **Parimon T et al., AJRCCM 175:712, 2007**

Phase IIb budesonide trial

DCP Phase IIb Trial of Inhaled Budesonide in Bronchial Dysplasia

112 smokers with dysplasia by bronchoscopy

↓ Helical CT

Screened (sputum): 1040
Cancers detected: 13

Budesonide vs. Placebo x 6mths

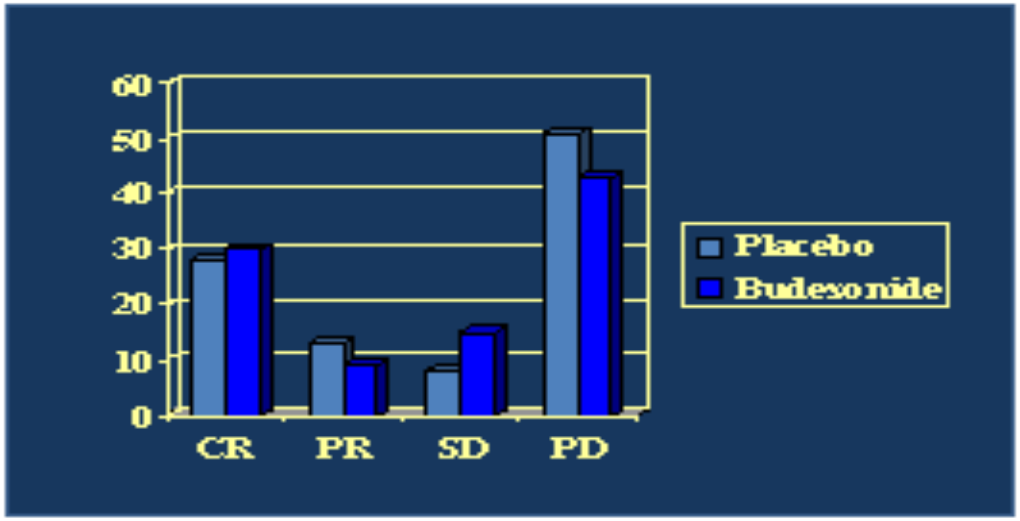
↓ Bronch, Spiral CT)

1° Endpoint: bronchial dysplasia (#sites/grade)
2° Endpoints: multiple biomarkers

Lam et al., Clin Cancer Res 2004;10:6502

Bronchial dysplasia

Phase IIb Trial of Inhaled Budesonide in Bronchial Dysplasia



- **Bronchial dysplasia – no effect of 6 mth Rx**
- **CT-detected lung nodules - 27% vs. 12% resolved (p=0.024)**

Lam et al., Clin Cancer Res 2004;10:6502

Chemoprevention trialPhase IIb Trial

Peripheral Lung Carcinogenesis Trial Design
Phase IIb Budesonide Chemoprevention Trial

202 participants with persistent LD-CT-detected peripheral nodules

↓ Randomize

inhaled budesonide vs. placebo x 1 year

↓

repeat LD-CT

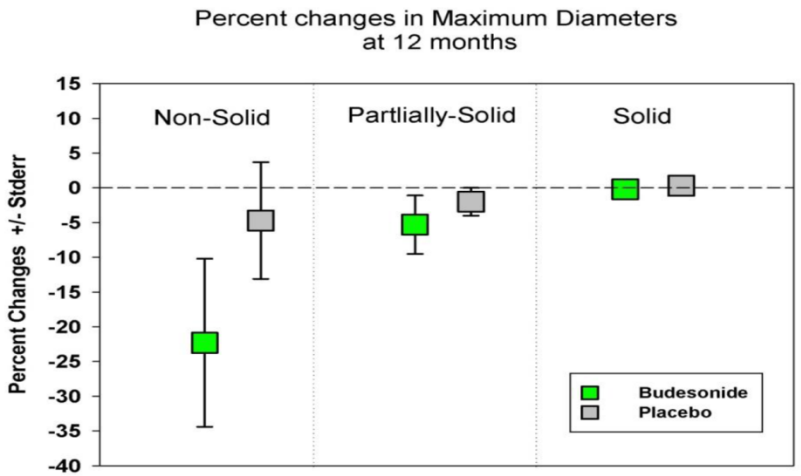
Primary endpoint: shrinkage of lung nodules

-*Veronesi et al., Cancer Prev Res 2011;4:34-42*

Chemoprevention Trial

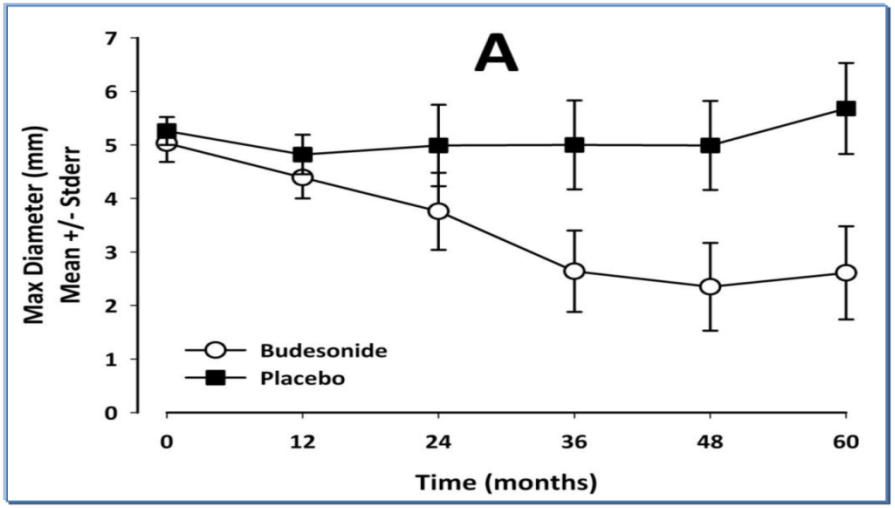
Phase IIb Budesonide Chemoprevention Trial
Lesion Specific Analysis

12 months



5-yr f/u, non-solid

p=.029



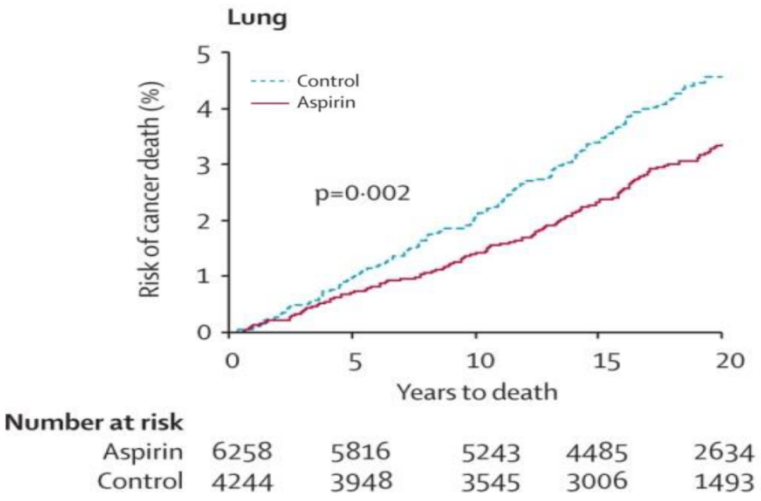
-Overall response negative, but trend toward regression in non-solid lesions (putative precursors of adenocarcinoma)

Veronesi et al., Cancer Prev Res 2011;4:34-42
Veronesi et al., Ann Oncol 2015;26:1025-30

Aspirin and Mortality

Effect of Aspirin on Lung Cancer Mortality

-Rothwell et al., Lancet 2011;377:31



-individual patient data from trials of ASA vs. none

-lung:

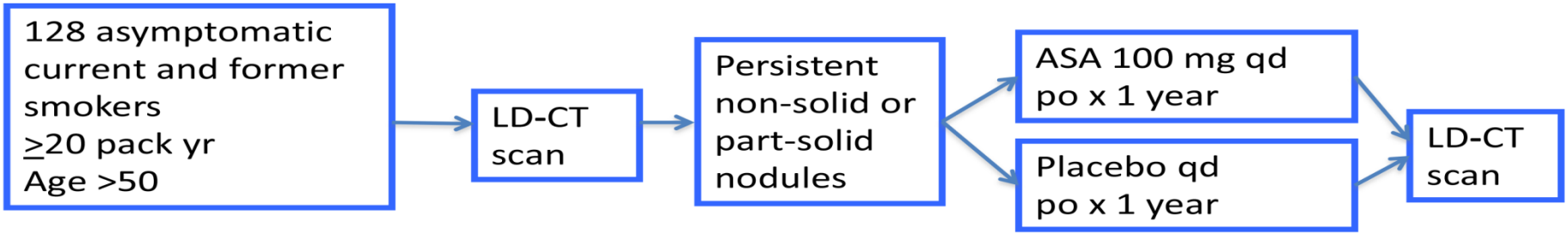
f/u	0-10 yrs	0-20 yrs
HR	0.68	0.71
	(0.50-0.92, p=0.01)	(0.58-0.89, p=0.002)

-adenocarcinoma only

-benefit only after 5 yrs

Phase II Trial

A Randomized Phase II Trial of Low Dose Aspirin versus Placebo in High-Risk Individuals with CT Screen Detected Subsolid Lung Nodules
PIs: Giulia Veronesi, MD and Bernardo Bonanni, MD; IEO

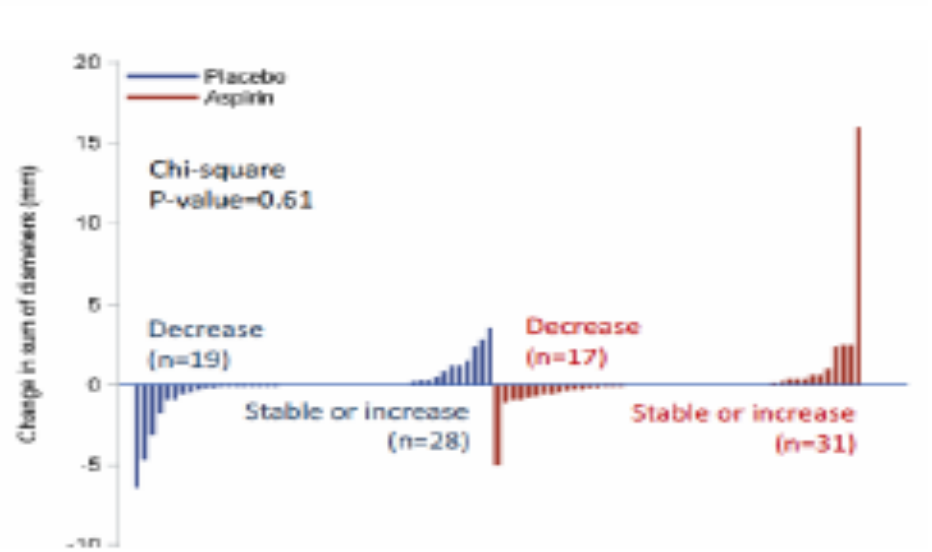


1° Endpoint: #/Size semisolid lung nodules
2° Endpoints: COX/LOX urinary metabolites (hs-CRP, PGEM, LTE4), miRNA signature, nodule-based endpoints

Accrual as of October 15, 2015: 47 participants

Aspirin trial

Phase II Trial of Low Dose Aspirin Trial



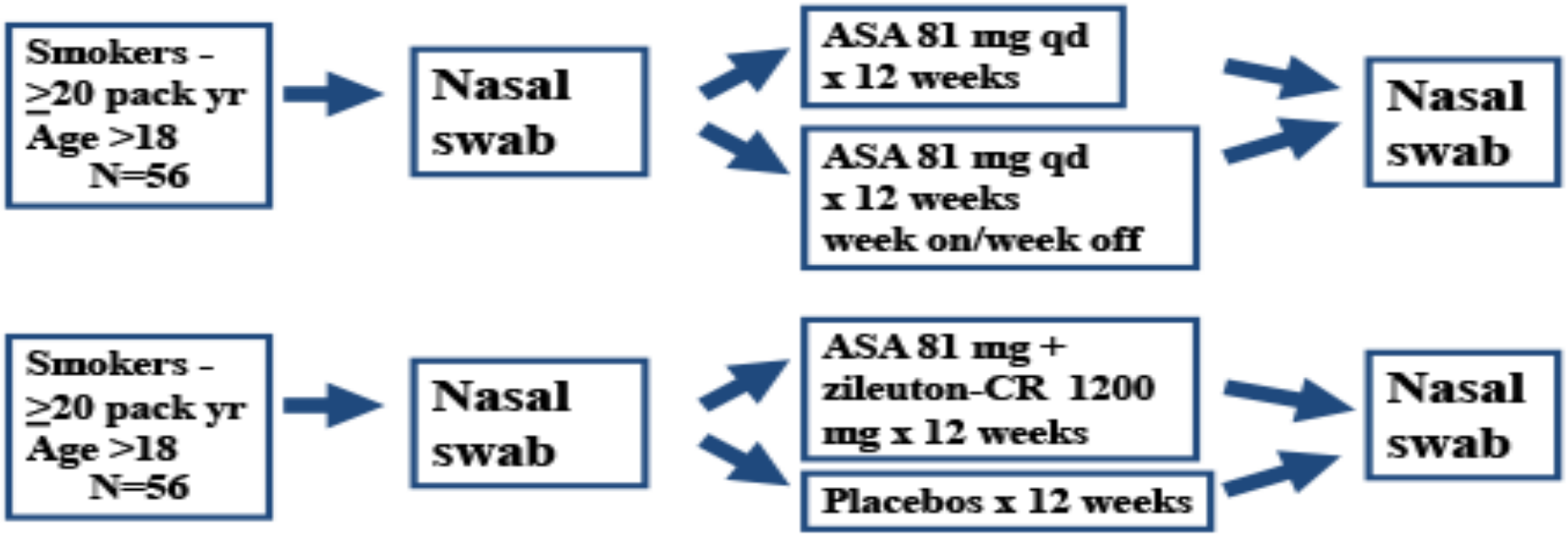
-98 participants randomized
-no difference in nodule size, new nodules
-no differences by sex, smoking status
-underpowered to detect differences in new cancers

Serrano D et al., JNCI Cancer Spectrum 2020 epub

Biomarkers

Biomarker Aspirin Chemoprevention Trials

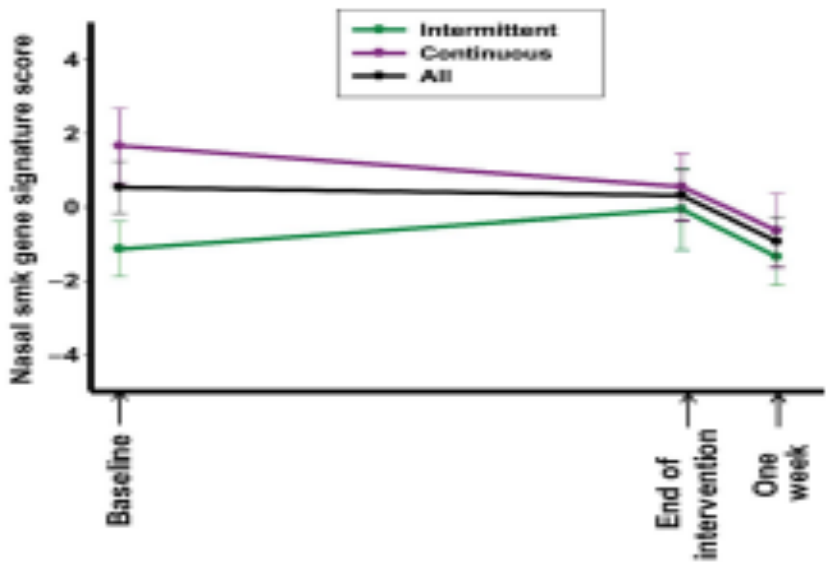
Linda Garland, University of Arizona

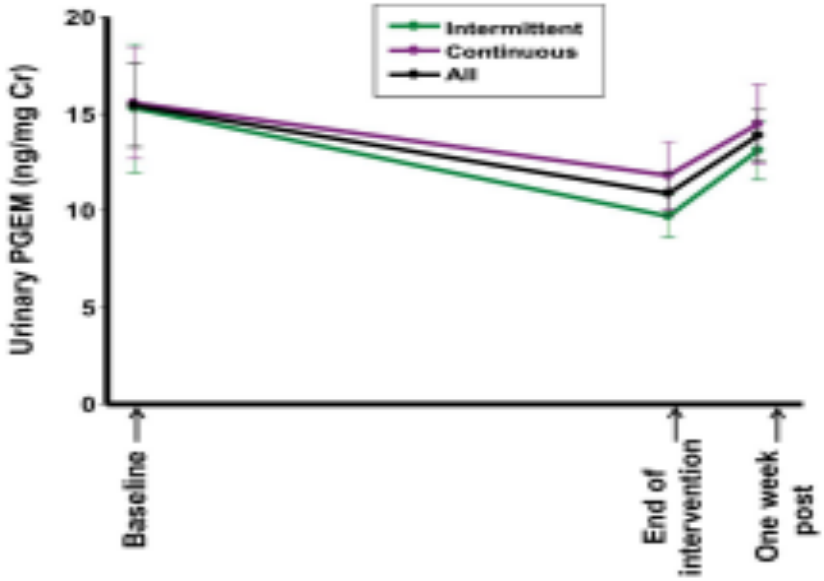


1° Endpoint: smoking gene expression signature (nasal epithelium)
2° Endpoint: PI3K gene expression signature, lung cancer gene expression Signature, COX/LOX urinary metabolites (PGEM, LTE4)

Minimal effects

Minimal Effects of Continuous vs. Intermittent Aspirin on Nasal Smoking Gene Signature Score

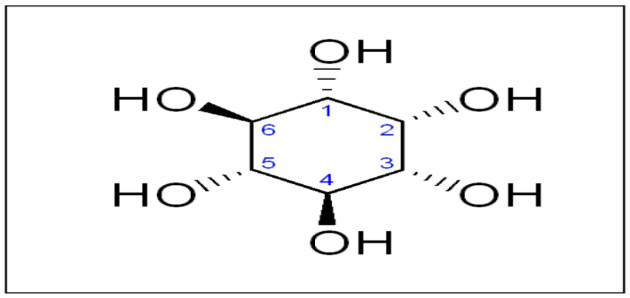




Garland LL et al. Cancer Prev Res 2019;12:809-820

Myo-Inositol

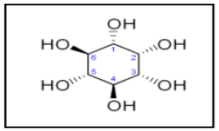
myo-Inositol



- Glucose isomer
- Source of several second messengers & signaling molecules
- Dietary sources (grains, beans, fruits, rice)
- Studied in psychiatric conditions (+/–), diabetic neuropathy(+/–), polycystic ovary syndrome (+)

Phase I Study of myo-Inositol

Phase I Study of *myo*-Inositol in Bronchial Dysplasia



- **Inhibits B[a]P carcinogenesis in mice (53%); combination with budesonide ↑↑**
- **Phase I study (26 participants)**
  - **tolerable 18 g/d**
  - **91% vs. 48% regression dysplasia, P=0.014 (10 participants)**

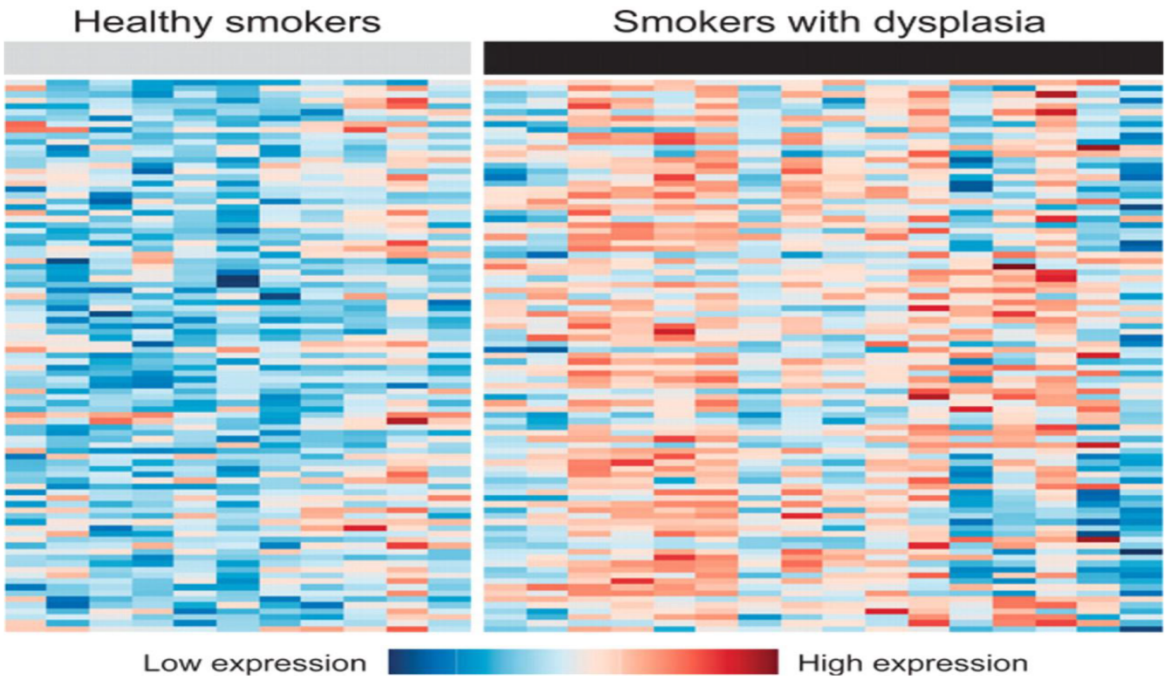
Table 5. Changes in pathologic grades of bronchial biopsy samples at baseline and after 3 months of *myo*-inositol (18 g): Lesion-specific analysis

Pathologic grades of bronchial biopsies at baseline	Status after 3 months of treatment			
	N	Stable	Regression*	Progression†
Placebo group (from ref. 18)				
Normal/hyperplasia/metaplasia	256	219	0	37
Mild dysplasia	134	72	62	0
Moderate/severe dysplasia	13	5	8	0
myo-Inositol group				
Normal/hyperplasia/metaplasia	38	36	0	2
Mild dysplasia	10	1	9	0
Moderate/severe dysplasia	1	0	1	0

Lam et al., CEBP 2006;15:1526

PI3K pathway genes**Phase IIB myo-Inositol Trial**

Increased Expression of Genes Induced by PI3K Pathway Activation in the Airway of Smokers with Dysplasia



-PI3K pathway is activated in smokers with dysplasia in airway p<0.001

-Myo-inositol inhibited PI3K activation in normal bronchial airways in smokers with regression of dysplasia (p=0.04)

Gustafson et al., *Sci Transl Med* 2010

Myo-Inositol in Bronchial Dysplasia

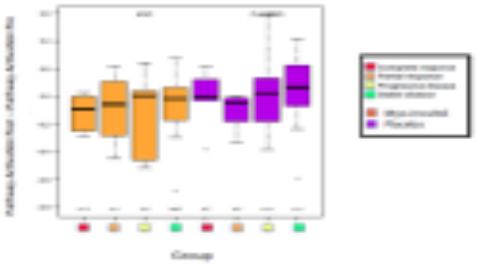
Phase IIb Study of *myo*-Inositol in Bronchial Dysplasia

Trial overview

- Age 45-74 years; ≥30 pack yr smoking; ≥1 dysplastic lesion
- *myo*-inositol 9g bid vs. placebo x 6 mths
- 1° endpoint:
  - Δ in dysplasia at 6 mths, per participant
- 2° endpoints:
  - -Ki-67
  - -blood/BAL biomarkers
  - -PI3K airway gene signature

Results (1° endpoint)

- 85 pts randomized, 74 evaluable for efficacy (*myo*-inositol n=38; placebo n=36)
- CR rate 26.3% vs 13.9%; PD 47.4% vs 33.3% (*myo*, placebo), p=0.76
- 2° endpt: ↓AKT activation in complete responders only
- 2° endpt: ↓IL-6 in BAL



Lam S et al. Cancer Prev Res 2016;9:906

Targeting inflammation

Targeting Inflammation/IL-1β

CANTOS Trial *Secondary Analysis*

- **Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS)**
  - 10,061 patients with atherosclerosis, hsCRP≥2 mg/L
  - Dose: 50 mg, 150 mg, or 300 mg sc q3mths vs placebo
  - Median f/u 3.7 yrs
- **Results:**
  - Dose-dependent IL-6 reduction 25-43% ($p<0.0001$)
  - Total cancer mortality: HR, 0.49 [95%CI, 0.31-0.75]-300 mg
  - Lung cancer mortality: HR, 0.23 [95%CI, 0.10-0.54]-300 mg
  - Lung cancer incidence: HR, 0.33/0.61 ($p<0.001$)-300/150 mg
  - No difference in overall survival (↑infection/sepsis)

Note: FDA declined to approve canakinumab for CV indication

Ridker PM et al. Lancet 2017;390:1833

Lung Carcinogenesis

The Continuum of Lung Carcinogenesis

Opportunities for Intervention

Normal → Hyper/Metaplasia → Dysplasia → Early-Late Cancer

Prevention

Early Detection

Treatment

Lung Cancer Screening

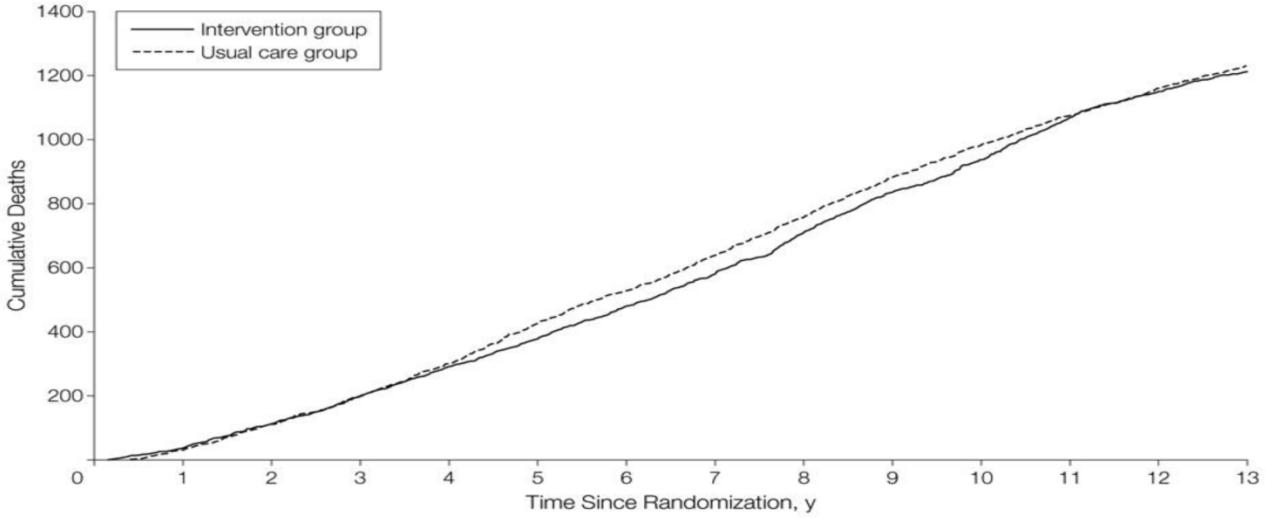
Issues in Lung Cancer Screening

- **Lead-time bias** = earlier diagnosis but no postponement of death (survival appears longer)
- **Length bias** = diagnosis of more indolent disease with longer preclinical phase (better prognosis, better outcome)
- **Overdiagnosis** = identification of clinically unimportant lesions that would not be diagnosed otherwise
- **Morbidity/mortality/cost of screening and subsequent work-up**

PLCO Trial

PLCO CXR Randomized Trial - Mortality

154,901 participants, PA CXR vs. usual care x 4 screens, 13 yr f/u



Intervention group													
Cumulative deaths	36	113	196	292	378	480	582	711	838	937	1070	1150	1213
Cumulative person-years	77 268	154 053	230 270	305 833	380 691	454 773	527 937	600 004	670 274	735 098	789 540	832 441	864 227
Usual care group													
Cumulative deaths	30	111	198	301	426	527	639	761	884	987	1076	1162	1230
Cumulative person-years	77 286	154 116	230 348	305 902	380 725	454 719	527 804	599 790	669 955	734 523	788 854	831 678	863 330

Oken, MM et al. JAMA 2011;306:1865-73

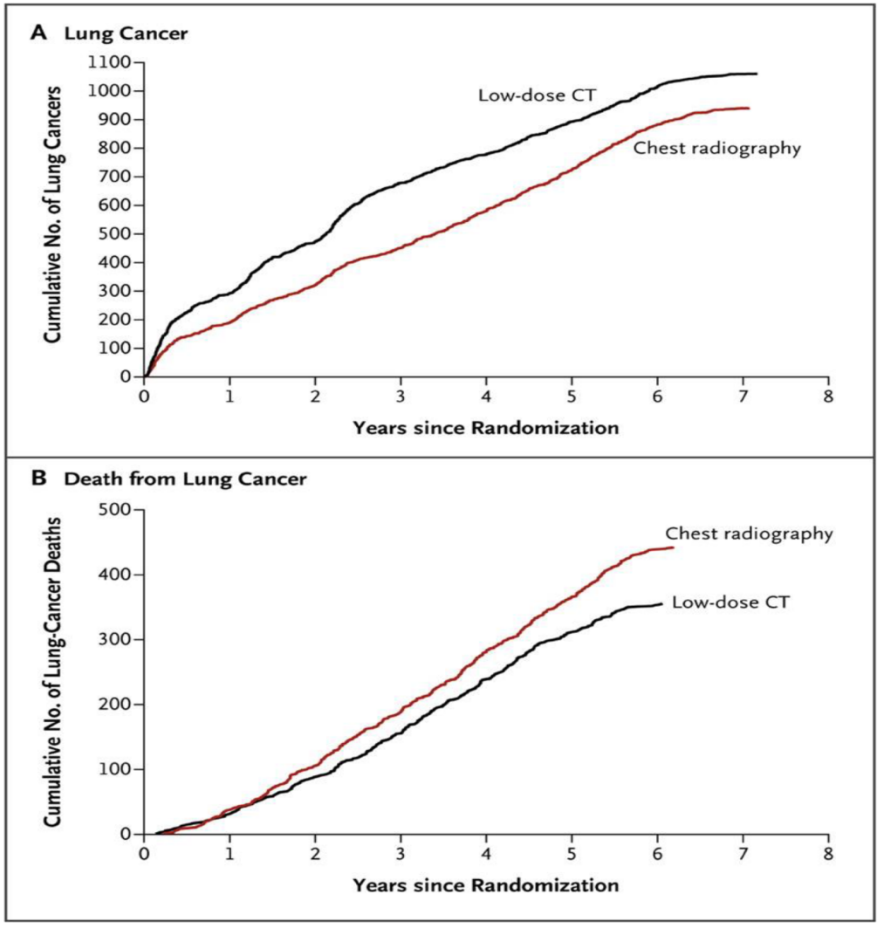
NLST (National Lung Screening Trial)

- **NLST design**
  - **53,454 smokers (current and former)**
  - **30 pack-yr smoking hx; quit ≤15 yrs ago**
  - **Age 55-74**
  - **Helical CT vs. chest X-ray (prevalence, then x2)**
- **NLST results**
  - **CT - 24.2% 'positive' tests, 354 lung cancer deaths**
  - **CXR – 6.9% 'positive' tests, 442 lung cancer deaths**
  - **20.0% reduction in lung cancer mortality**
  - **6.7% reduction in all cause mortality**

NLST Research Team. N Engl J Med 2011;365:395-409

Lung Cancer and Deaths

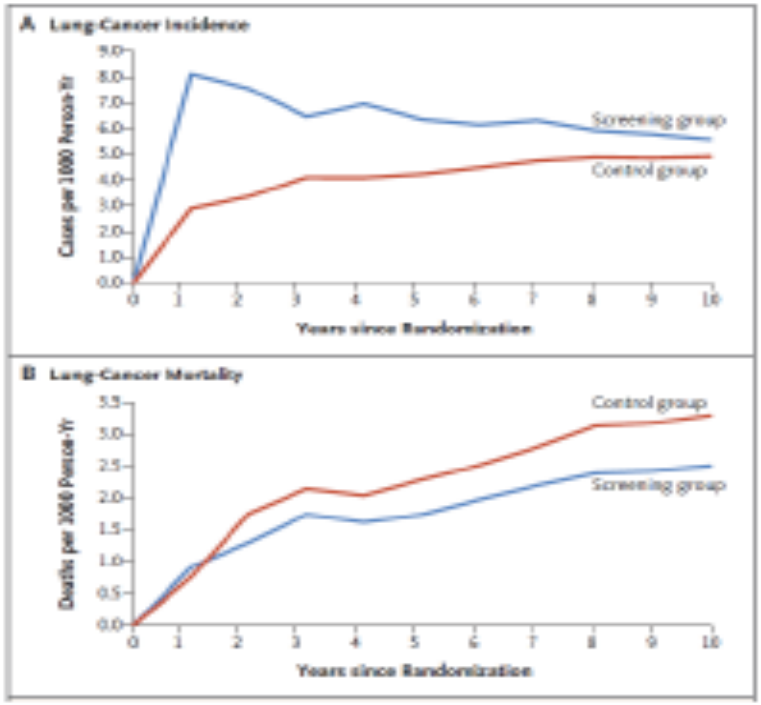
Cumulative Lung Cancers and Deaths from Lung Cancer



NLST Research Team N Engl J Med 2011;365:395-409

CT screening

NELSON CT Screening Trial



- 13,195 men and 2594 women
- age 50-74
- Screening baseline, yr 1, yr 3, yr 5.5
- Volumetric analysis
- 10 yr follow-up
- Men: RR=0.76
- Women: RR=0.67

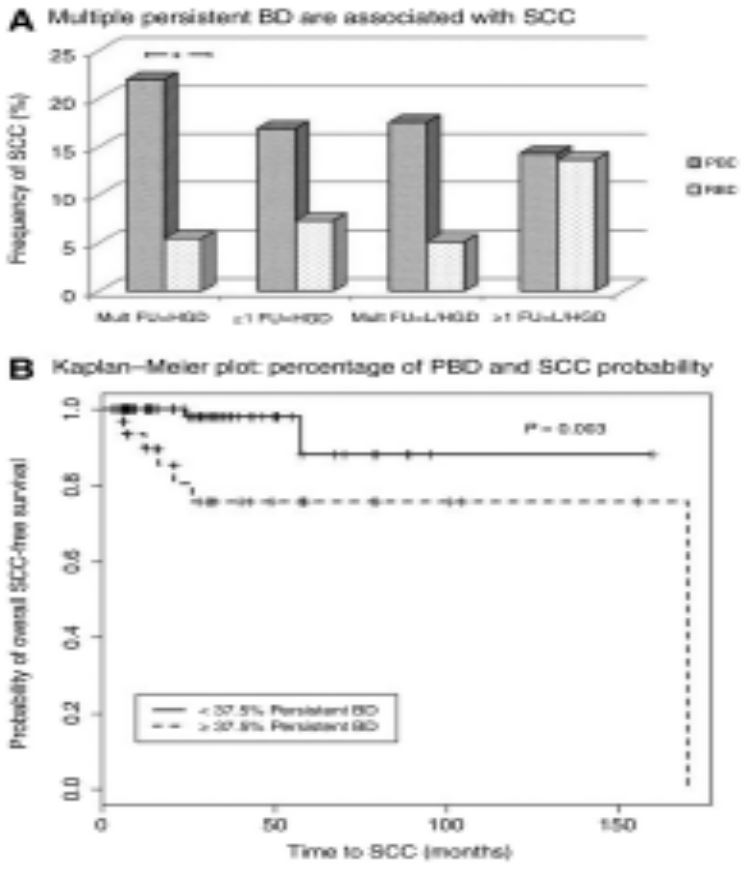
Moving forward

How do we move forward? What are the opportunities?

- **Understand the biology and natural history of carcinogenesis**
  - Understanding natural history of premalignancy - TCGA of premalignancy (PCA)
    - Who progresses, who doesn't?
    - Target deregulated processes driving carcinogenesis (not just mutations)
    - Harness the immune response
- **Improved clinical trials – e.g., sample the field using 'omic' technologies**
  - To detect drug effects on deregulated pathways in a short time frame
  - Role of liquid biopsy?
- **Focus on at-risk (molecularly?) homogeneous cohorts**
- **Consider the entire person, at risk for multiple cancers and chronic diseases**
- **Multiple early phase trial designs to build a "body of evidence" to justify phase III**

Bronchial Dysplasia

Progression vs. Regression of Premalignant Lesions: Bronchial Dysplasia



- Persistent bronchial dysplasia is associated with sq cell ca.
  - multiple follow-ups with high grade dysplasia
- Persistence or progression to high grade 7.8-fold increased risk of inv sq cell
- Molecular analyses pending

Merrick et al. Cancer Prev Res 2016;9:96-104

Summary

Summary

- **Tremendous progress has been made in understanding lung carcinogenesis**
  - **Pathologic classification oversimplifies molecular complexity**
    - **Heterogeneity in tumors and premalignant lesions complicates efforts to intervene**
  - **Precision medicine applicable to significant (but small) subset of advanced stage patients, increased survival**
  - **Early days of immunotherapy – prolonged survival in small subset of patients**
    - **Applications to prevention not yet clear**
  - **Early detection with helical CT – decreased lung cancer mortality**
  - **New targets and tools available for chemoprevention research**

“An ounce of prevention is worth a pound of cure”

-Benjamin Franklin

Acknowledgments

Acknowledgments

- DCP Phase II Consortia Program
- Stephen Lam, British Columbia Cancer Agency
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